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Audit of the Frequency and Clinical Response to Excessive Oral Anticoagulation in an Out-Patient Population

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A retrospective review of over-anticoagulated patients with critical international normalized ratios (INRs) was undertaken in a large outpatient laboratory. In the six-month study period, 85 prothrombin times (PTs) were identified with an INR of ⩾6.0, an overall incidence of elevated PTs of 0.2% or two per 1,000 INR tests. Complete follow-up data was available on 65 patients. When compared to an age- and gender-matched control group without INR ⩾6.0, high-INR patients were significantly more likely to manifest the presence of alcoholism or liver disease, to have been anticoagulated for less than six months, to have experienced more frequent warfarin dosage changes, and to have had the addition of a medication known to interact with warfarin. In the high-INR group, a likely cause for the specific critical INR was identified in 44 patients (68%). Drug interactions followed by compliance problems were the most common factors identified. The 13 patients (20%) who received vitamin K therapy experienced no difference in the clinical outcome compared with those managed conservatively. Conservative management of critically high INR values appeared to be as efficacious as intervention with vitamin K therapy. Am. J. Hematol. 59:22–27, 1998. © 1998 Wiley-Liss, Inc.

Key words: prothrombin time; INR monitoring; oral anticoagulant therapy; vitamin K therapy; warfarin; induced bleeding

INTRODUCTION

Although oral anticoagulants are widely prescribed, the narrow therapeutic window associated with their use means that frequent monitoring is necessary and over-anticoagulation can be dangerous [1,2]. There have been few studies which have attempted to investigate the etiology and clinical course of a cohort of patients on oral anticoagulant therapy subsequently identified as out-of-control. Both the American College of Chest Physicians (ACCP) and the British Committee for standards in Hematology (BCSH) have published recommendations regarding the management of over-anticoagulated patients; however, no uniform consensus exists in this regard [3,4]. The principal purpose of this retrospective study involving a large out-patient laboratory was to determine the incidence and clinical outcome of over-anticoagulation. A second study aim was to attempt to determine possible causative factors for individual critical international normalized ratio (INR) values.

MATERIALS AND METHODS

Metro-McNair Clinical Laboratories (Island Division) is a large out-patient laboratory system servicing approximately 500,000 patients on Vancouver Island, British Columbia, Canada. Over a six-month period, from February to July of 1996, 29,000 prothrombin times

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(PTs) determinations were performed on patients receiving oral anticoagulant therapy. All PTs were performed on an MLA 1000 automatic microprocessor controlled autoanalyzer (Medical Laboratory Automation, Pleasantville, NY). PT determinations were performed within four hours of receipt of the specimen in the laboratory. The reagent system used was Innovin (Dade Baxter Diagnosis Reagents, Dade, FL) with an International Sensitivity Index (ISI) of 0.96. Individual INR values were reported up to 10.0. Above 10.0, INR values were recorded as >10.0.

During the six-month study period all patients with elevated INRs ⩾6.0 were identified. A control group matched for age and gender, but without an INR ⩾6.0, was otherwise randomly selected from the same patient population. In the case of all patients, individual follow-up was undertaken with the primary responsible physician. This physician was interviewed, and relevant data was abstracted from the patient's chart. Factors that were investigated besides age and sex of the patient included: The reason for oral anticoagulation; the duration of time the patient had been on oral anticoagulant therapy; the duration of time the patient had been stable on oral anticoagulant therapy before the critical INR value; the individual patient's therapeutic range; and various medications used other than oral anticoagulants. The presence of multiple medications was defined as the taking of four or more prescription drugs in addition to warfarin. The number of warfarin dosage changes prior to the out-of-control INR value was also abstracted for the high-INR group, and the total number of warfarin dosage changes was abstracted for the control group. In the high-INR group, patient management subsequent to the discovery of the high INR was documented and the use of corrective vitamin K therapy was also noted. Any bleeding complications subsequent to the high-INR episode were documented. Major bleeding was defined as bleeding requiring either transfusion or hospitalization. The duration of time required for the patient to return to stable anticoagulant control within the therapeutic range was also detailed. In the high-INR group, return to stability within the therapeutic range was defined as the length of time taken to achieve two or more results within the therapeutic range following the critical INR value. Statistical analysis comparing the high-INR group with the controls in terms of characteristics of the study population was performed using contingency table analysis using the chi–square test or the Mann-Whitney U–Wilcoxon rank sum tests for non-parametric results. Comparison of the various factors associated with a variable anticoagulation response between the two groups was performed using logistic regression analysis.

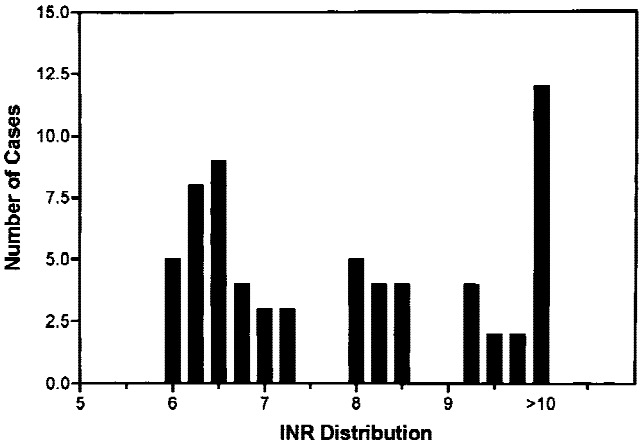

Fig. 1. The range of INRs in 65 patients.

RESULTS

In the six-month study period, 29,000 PTs were performed on patients receiving oral anticoagulation. Eighty-five PTs were identified with an INR of ⩾6.0, an overall incidence of elevated PTs of 0.2%. In investigating the 85 patients with INR ⩾6.0, it proved possible to perform detailed follow-up on 65. The individual critical INRs in this patient group are plotted in Figure 1. The median INR was 7.3 (range 6.0–>10.0). The demographics of the high-INR group and the control group are presented in Table I. Only 46 (71%) of the high-INR group vs. 59 (91%) of the control group had been taking anticoagulant therapy for six months or longer—a statistically significant difference. The reasons for anticoagulation were generally similar within the high-INR group and control group except in the case of artificial heart valves or atrial fibrillation in which statistically, significantly more patients had artificial heart valves or atrial fibrillation in the high-INR group.

Data on INR monitoring in the high-INR group and control group are presented in Table II. In the control group, the majority of patients were being monitored at either two weekly or monthly intervals. In the high-INR group during the six month period, if PT results were stable, most patients were monitored at twice weekly to monthly intervals. For the majority of high-INR patients, this changed to twice weekly or weekly once instability had been detected.

When compared to the high-INR group, the control group had a lower median number of total INR determinations, a lower number of INRs below therapeutic range as well as above therapeutic range, and a higher median number of INRs within the therapeutic range; all of these comparisons were statistically significant. The median number of warfarin dosage changes was three in the high-INR group vs. one in the control group, which was also statistically significant.

TABLE I. Characteristics of Study Population*

	High INR group	Control group	*P*-value
Patients—No (%)	65 (100)	65 (100)	
Men	32 (49)	32 (49)	
Women	33 (51)	33 (51)	
Age in year—median (range)	74 (28–90)	74 (28–90)	
Reason for anticoagulation			
Atrial fibrillation	30 (46)	45 (69)	.0078
Artificial heart valve	19 (29)	6 (9)	.0038
Stroke	7 (11)	10 (15)	.4351
Venous thrombosis	4 (6)	5 (8)	1.0
Pulmonary embolus	4 (6)	3 (5)	1.0
Mitral stenosis	2 (3)	—	N/A
Myocardial infarct	2 (3)	1 (2)	1.0
Miscellaneous	2 (3)	2 (3)	1.0
Arterial thrombosis	0 (0)	3 (5)	.2241
Duration of anticoagulation			
≤1 month	6 (9)	1 (2)	.1148
>1 month	59 (91)	64 (99)	.1148
>6 months	46 (71)	59 (91)	.0038

*INR, international normalized ratio, N/A, not applicable.

TABLE II. INR Data—Study Population*

Frequency of INR monitoring No (%)	High INR group	Control group	*P*-value
Stable phase			
Weekly	18 (28)	6 (9)	N/A
2 Weekly	20 (31)	23 (35)	
3 Weekly	8 (12)	13 (20)	
4 Weekly	17 (26)	20 (31)	
>4 Weekly	1 (1)	3 (5)	
Unstable phase			
Daily	3 (5)		
Twice weekly	28 (58)		
Weekly	24 (37)		
6 Month INR data—median (range)			
Total INR determinations	12 (1–42)	9 (3–29)	.0047
Number of INRs in therapeutic range	4 (0–13)	6 (1–27)	<.0001
Number of INRs below therapeutic range	5 (0–23)	2 (0–9)	<.0001
Number of INRs above therapeutic range	2 (0–12)	0 (0–4)	<.0001
Mean number of warfarin dosage changes	3 (0–24)	1 (0–6)	<.0001

*INR, international normalized ratio, N/A, not applicable.

The presence of individual factors within the high-INR group and the control group previously associated in the literature with a variable anticoagulant response is detailed in Table III. A linear logistic regression analysis comparing the high-INR group to the control group showed that the presence of alcoholism or liver disease, multiple warfarin dosage changes, and the addition of a new drug known to be capable of interacting with warfarin, were significant variables. When examining patients with at least one risk factor as well as multiple risk factors, there was, again, a statistically significant difference between the high-INR group and the control group. In the high-INR group, 58 patients (89%) had at least one risk factor versus 34 patients (52%) in the control group. In the case of multiple risk factors, 38 patients (59%) in the high-INR group vs. 12 patients (19%) in the control group had multiple risk factors.

TABLE III. Presence of Factors Associated With a Variable Anticoagulation Response*

Variable individual risk factors	No (%) high INR group	No (%) control group	*P*-value
Duration of therapy <1 month	5 (8)	1 (2)	.1316
Multiple warfarin dosage changes (>4 over 6 months)	23 (35)	5 (8)	.0004
Addition of a new drug potential for interaction	23 (35)	4 (6)	.0002
Taking multiple medications (>4)	34 (52)	24 (37)	.0531
Congestive heart failure	18 (28)	12 (19)	.2142
Alcoholism/liver failure	14 (22)	1 (2)	.0064
Impaired renal function	8 (12)	3 (5)	.1293
Malnutrition	7 (11)	0	.7158
Patients with at least one risk factor	58 (89)	34 (52)	<.0001
Patients with multiple risk factors	38 (59)	12 (19)	<.0001

*INR, international normalized ratio.

Twenty-four patients (32%) in the control group vs. 34 patients (52%) in the high-INR group were consuming multiple medications: Not a statistically significant difference. The median number of medications taken in both groups was six (range five to 14 in the high-INR group, range five to 11 in the control group).

In the high INR group, it proved possible to identify a probable cause for the out-of-control episode in 44 patients (68%). A breakdown of presumed causes is included in Table IV. Drug interactions in 28 patients (43%) and problems with compliance in 18 patients (28%) were the most common factors. In the category of decompensating systemic illness, there were two patients with terminal cancer, another patient with septic shock and hypotension, and a fourth patient had a wasting illness with fever of unknown origin.

In the control group, the four drugs which had been introduced with known potential for warfarin interaction included Tegretol, doxycycline, Indocid,® and allopurinol. In the high-INR groups, after antibiotics (11 cases), the drugs most commonly implicated included fenofibrate (3 cases), cimetidine (2 cases), prednisone (2 cases), and one case each involving cholestyramine, sotalol, theophylline, propafenone, and amiodarone. The majority of drug interactions fell into the category of potentiation of warfarin activity.

For the high-INR group, physician management of individual high-INR episodes, as well as bleeding complications, is detailed in Table V. Seven patients experienced bleeding complications. Major bleeding requiring

TABLE IV. Probable Cause of Critical INR Results in 65 Patients*

Variable	No[a] (%)
Drug interaction	28 (43)
Unknown	21 (32)
Compliance problem	18 (28)
Alcohol/liver disease	8 (12)
New therapy	4 (6)
Decompensating systemic illness	4 (6)
Inappropriate warfarin dosage change	2 (3)
Malabsorption/dietary	2 (3)

*INR, international normalized ratio.
[a]Total exceeds 65 as several patients had more than a single contributing factor.

TABLE V. Vitamin K vs. Conservative Therapy Data*

	Conservative therapy group No (%)	Vitamin K therapy group No (%)
Patients	52 (80)	13 (20)
Median INR (range)	7.0 (6.0–>10.0)	>10.0 (6.8–>10.0)
Bleeding on presentation	4 (6)	3 (5)
Major	1 (2)	1 (2)
Minor	3 (5)	2 (4)
Bleeding after warfarin stopped	0	0
Number of days warfarin withheld		
Day 1	5 (10)	1 (8)
Day 2	21 (40)	4 (30)
Day 3	15 (29)	5 (39)
After day 3	11 (21)	3 (23)
Timing of first follow-up PT test		
Day 1	14 (27)	4 (30)
Day 2	5 (10)	1 (8)
Day 3	10 (19)	2 (15)
After day 3	23 (44)	6 (46)

*INR, international normalized ratio; PT, prothrombin time.

hospitalization included one episode of rectal bleeding (patient subsequently was found to have colon cancer), and a case of mesenteric hemorrhage. Minor bleeding, included one case each of hemoptysis, epistaxis, and hematuria, and three cases of purpura and hematomas. Thirteen patients (20%) were treated with vitamin K. Individual doses of vitamin K included one mg subcutaneous (five patients), three mg subcutaneous (one patient), 10 mg orally (four patients) and 10 mg subcutaneous (three patients). Following the critical INR value, the majority of patients had warfarin therapy withheld for 2–3 days. In each group, approximately 40% of patients had a PT repeated within the first two days after cessation of warfarin therapy. The clinical outcomes appeared similar between the group of patients who received vitamin K and those who did not. No patient in particular in either group experienced further bleeding complications once warfarin therapy had been stopped. The average time for individual patients to return to therapeutic control is illustrated in Figure 2. The vitamin K treated patients did not

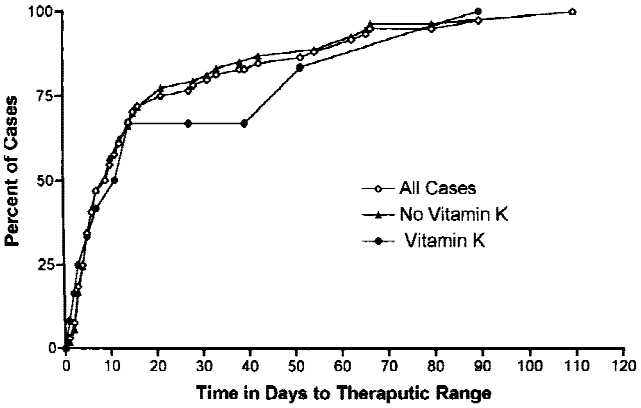

Fig. 2. The duration of time in days required to return to stable anticoagulant control within the therapeutic range for the two patient groups.

appear to achieve stable therapeutic control more rapidly than those who did not receive vitamin K. Overall, approximately 50% of patients had not returned to stable therapeutic control by the end of the first week post-high INR. With further follow-up, the figures were: 14 patients (22%) and seven patients (11%) at four weeks and eight weeks, respectively.

DISCUSSION

Whereas a number of authors have examined the overall quality of anticoagulation control in large clinic populations, there have been relatively few studies which have reported on the management and clinical outcome of poor anticoagulation control, or attempted to identify likely responsible factors [5,6]. In studies which have investigated the relative number of patients in control in an attempt to define the quality of oral anticoagulant management, the figure has varied from 40–70% [7–9]. With the current study involving 29,000 PT results over a six-month period, only 0.2% with an INR $\geqslant$6.0 were identified. These data imply that the vast majority of patients followed up by the laboratory were in good anticoagulant control.

In comparing the high-INR group to the control group, the high-INR group contained significantly more patients with artificial heart valves and atrial fibrillation. Since some patients with artificial heart valves are run at a higher INR range (2.5 to 3.5 vs. 2.0 to 3.0), this might possibly have been a factor relating to the out-of-control episode. However, there is no evidence that patients with heart valves or atrial fibrillation are intrinsically more difficult to manage with oral anticoagulant therapy. There is no consensus on the optimal frequency of INR monitoring for individual patients stable on oral anticoagulant therapy [2,4]. The two-to-four week interval observed for most patients in the control group and the

high-INR patients in the stable phase and weekly or twice weekly monitoring that was performed following the detection of the critical INR value in the high INR group are compatible with protocol at many large anticoagulation clinics [9,10].

A variety of factors have been postulated in the literature as predisposing to variable anticoagulant control. Shepherd et al. [6] identified the duration of treatment as a consideration, as well as patient age. On the other hand, other investigators specifically found that in elderly patients, variability of anticoagulation control was not influenced by age, sex, social status, mobility, visual acuity, domiciliary supervision of medication, or the indication for anticoagulation [11,12]. A significant correlation has been observed between the presence of concomitant drug therapy and the degree of anticoagulation control, but not necessarily with the occurrence of treatment failures [11,13]. Alcoholism and alcoholic liver disease have been associated with a variable anticoagulant response [3]. Landefelt and Beyth [1] identified a number of risk factors for poor anticoagulant control including the first month of therapy and the presence of serious comorbid disease, especially cerebrovascular, kidney, heart, or liver disease. Fihn et al. [14] implicated repeated variation in warfarin dosage as critical, in that a change in warfarin dosage as infrequent as three or four times a year constituted significant risk for future unstable control and anticoagulation-associated bleeding.

The results of the current investigation are consistent with these observations in that the high-INR group had statistically significant differences in relation to postulated risk factors when compared with the control group. Compared to the control group, the patients with high INRs were more likely to have experienced a shorter duration of anticoagulant therapy and appeared to have had a significantly higher incidence in the fluctuation of oral anticoagulant control with more INRs above or below the therapeutic range than were actually in the therapeutic range during the six-month study period. The high-INR group had also received significantly more frequent warfarin dosage changes during the study period as compared to the control group (median three vs. one). With regard to other factors previously reported to be associated with a variable anticoagulant response, linear logistic regression confirmed that the presence of alcoholism or liver disease, as well as multiple warfarin dosage changes and the addition of a new drug known to interact with warfarin, were significant variables. Moreover, the high-INR group had a significantly increased number of patients with both single and multiple factors.

In the current study, a significant number of patients in both the high-INR group and control group were taking multiple medications, with the median number of six medications other than warfarin in both groups. This finding was not surprising given the age of the study population.

In terms of a most likely causative factor for individual critical INR results, Kumar et al. [15], in a prospective study, found that poor compliance was a major consideration in a group of patients previously noted to be unstable. In another retrospective study of 45 patients with INRs >8.0, principal factors that appeared to contribute to the out-of-control incident included infection or antibiotic therapy, failure to recognize disseminated intravascular coagulation, other drug interactions, or the presence of liver disease [5]. The current study results are compatible with earlier investigations in that drug interactions, followed by problems with compliance, appeared to be the major causes for critical INR values. Among drugs, antibiotics were the most common agents, followed by alcohol. A frequent clinical scenario involved a patient who was started on broad spectrum antibiotics for an upper respiratory or urinary tract infection by an alternative physician who presumably was unaware of the oral anticoagulation status.

It is interesting to speculate on the possible etiology underlying the critical INRs in the patients in whom no precipitating factor was apparent. Variations in vitamin K intake have been implicated in poor oral anticoagulant control [16,17]. Although it has been estimated that the average daily consumption of vitamin K in North America is in the range of 300 μg, there is evidence that for many of the elderly, this value is considerably less [18]. Such individuals may be at particular risk for any significant change in their overall vitamin K intake. The use of a vitamin K questionnaire has been advocated in unexplained cases of poor anticoagulant control once other factors have been ruled out [19].

The actual INR level which constitutes a risk for increased bleeding has been debated [3,4]. Studies have suggested that there is an inconsistent bleeding risk for INR values $\leqslant$5.0 in that, below an INR of 5.0, there appears to be little apparent increase in bleeding risk over what is experienced by patients within the therapeutic range [20,21]. The optimum management of patients with prolonged INRs is also currently under review [3,4]. The ACCP recommendations suggest that, for an INR of <6 with no associated bleeding, intervention is not necessary [3]. For an INR greater than six but less than 10, a small dose of 1–2 mg of vitamin K may be given. If the INR is >10 and the patient is not bleeding, a larger dose of vitamin K (three mg) should be used. With serious bleeding or major warfarin overdose (defined as an INR of >20), 10 mg of vitamin K is recommended, supplemented with factor concentrate or fresh-frozen plasma. Recommendations for the use of vitamin K in patients who have elevated INRs but are not bleeding represent a potential cause for concern since inappropriate use of vitamin K may render patients resistant to warfarin

therapy for several days and predispose them to serious recurrent thrombosis [2,22].

A recent retrospective study of 51 patients with INRs >6.0 compared patients who had received vitamin K to a conservatively treated group [22]. In this investigation, none of the patients in the conservatively treated group experienced significant hemorrhage and the clinical outcome was similar between groups. The results of the current study support this experience in that the clinical outcome was similar between patients receiving vitamin K and those who did not. Although potential physician intervention is obviously a significant contributing factor, patients who received vitamin K did not appear to experience a more rapid return to anticoagulation control compared with those who did not. A surprising study finding was the fact that 14 patients (22%) required greater than four weeks to return to therapeutic control whereas seven patients (11%) required greater than eight weeks. In these instances, physicians appeared to be excessively cautious in using an adequate dosage of warfarin following the initial high INR such that subtherapeutic INRs occurred for a prolonged period of time.

SUMMARY

In a group of 65 patients with INRs ⩾6.0 the incidence of hemorrhage was 11%. As opposed to the control group, patients within the high-INR group had a higher incidence of alcoholism or liver disease and were more likely to have been anticoagulated for less than six months, experienced more frequent warfarin dosage changes, and were more likely to have experienced the addition of a new drug known to interact with warfarin. A probable cause for the critical INR was identified in 58% of patients. The most common causes were drug interactions followed by problems with compliance. In this patient population, treatment with vitamin K did not appear to influence clinical outcome.

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